Remarks

Claims 1-13, 15-20, and 28-34 were pending in the subject application. Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 USC §112, second paragraph. By this Amendment, claims 1, 13, 28, and 34 have been amended, claims 7-10, 15, 20, and 32 have been cancelled, and new claims 35 and 36 have been added. Support for the new claim and amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-6, 11-13, 16-19, 28-31, and 33-36 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claims 1-9, 11-13, 16-19, and 28-34 remain rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Turgeman *et al.* (2001) and Juan *et al.* (2001). In addition, claim 10 remains rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Turgeman *et al.* (2001), and Juan *et al.* (2001), and further in view of Nicklin *et al.* (2002). The Examiner acknowledges that the Tang *et al.* reference does not teach a genetically modified stem cell or a nucleic acid sequence encoding a therapeutic product as recited in claim 1 of the subject application or a modified mammalian tissue as recited in claims 28-33. However, the Examiner relies on the Turgeman *et al.* reference for teaching genetically modified stem cells to express desired therapeutic proteins. The Juan *et al.* reference is relied on for teaching an HO-1 gene from adenoviral vector for therapeutic purposes. The Nicklin *et al.* reference is cited as teaching the use of adeno-associated virus (AAV) based vectors in gene therapy. The Examiner concludes that it would have been obvious to combine the teachings of the cited references to arrive at Applicants' claimed invention. Applicants respectfully traverse these grounds of rejection.

As an initial matter, Applicants note that claims 1 and 28 have been amended to incorporate the elements of dependent claim 10. Thus, §103 the rejection of claims 1-9, 11-13, 16-19, and 28-34 is rendered moot by this Amendment.

Applicants respectfully maintain that the cited references, whether taken alone or in combination, do not teach or suggest the claimed invention. Applicants respectfully maintain that the combination of a gene switch/biosensor and a gene amplification system provided in a stem cell

or a progenitor cell is novel and not obvious over the teachings of the cited references. Applicants' claimed invention advantageously provides for cell therapy wherein a patient can have their own stem or progenitor cells prepared from their own tissue (*e.g.*, bone marrow) and then the cells can be provided with a vector (*e.g.*, hypoxia gene switch/transgene) outside the body before injecting the modified cells directly into the target tissue (*e.g.*, heart) of the patient.

As Applicants have discussed in response to previous Office Actions, the claimed invention provides cells, such as adult stem cells derived from bone marrow, a novel and surprising means of surviving in a hostile environment (such as in an injured heart where oxygen levels are very low). When unmodified bone marrow stem cells are transplanted into ischemic hearts, the majority of the engrafted cells (over 90%) die within 1-2 days. Thus, it was not obvious to provide cells with means for surviving in the hostile environment because the high rate of death of implanted stem cells was not known in the art at the time of the present invention. Applicants respectfully assert that this point is not addressed in the current Office Action, nor is it taught or suggested in any of the cited references. In regard to this issue, the Examiner simply states in the current Office Action that "It should be emphasized that 'surviving in a hostile environment (such as in an injured heart where oxygen levels are very low)' is taught by the primary reference Tang *et al.*, not Turgeman *et al.*" The Examiner has not rebutted Applicants' assertion or pointed out where in any of the cited references, including Tang *et al.*, it is taught that stem cells transplanted into ischemic tissue have a high death rate (over 90%). Applicants respectfully note that a combination of elements is not *prima facie* obvious if an ordinarily skilled artisan would not have recognized an apparent reason to combine the elements. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007); *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335 (Fed. Cir. 2009). Applicants respectfully assert that there was no apparent reason to combine the elements because, as noted above, the high rate of death of implanted stem cells in a hostile tissue environment was not known in the art at the time of the invention.

Applicants also respectfully assert that it is only the present invention that solved the problem of poor cell survival that occurs in stem cell therapy. It is well settled in U.S. patent law that a patentable invention may lie in the discovery of a source of a problem. *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 US 45 (1923); *In re Sponnoble*, 160 USPQ 237 (CCPA 1969). None of the cited references, including the secondary references, teach or suggest anything of

relevance in regard to the problem of implanted stem cell survival and, thus, a person of ordinary skill in the art would not have been motivated to combine the exogenous first and second polynucleotide of the subject invention into a stem cell or a progenitor cell. The Fukuda (2003) reference newly cited in the current Office Action also does not teach or suggest that unmodified stem cells implanted into ischemic tissue have a high death rate. The Fukuda reference only discloses that a cardiomyogenic cell line could be isolated from bone marrow mesenchymal stem cells and discusses that such cells could *possibly* be used in cell transplantation therapy for heart failure. The Fukuda reference does not disclose that stem cells implanted in ischemic tissue have a very high death rate. Thus, an ordinarily skilled artisan at the time of the invention expected that implanted stem cells had a typical cell survival rate and, therefore, the artisan would **not** have been concerned with or motivated for finding ways to improve stem cell survival rate. It is only the subject application that teaches the problem and provides a solution to the problem in the form of the claimed invention.

The Tang *et al.* reference describes testing different types of gene switches, including single vector and double vector models. The rat myoblast cell line H9c2 referred to in the Tang *et al.* reference was only used for testing the vector. It was not used for stem cell transplantation. The authors of the Tang *et al.* reference did not teach or suggest an approach for improving stem cell survival when the cells are transplanted into injured tissue, such as ischemic heart tissue. The work reported in the Tang *et al.* reference is directed solely to development of an injectable gene switch which would reside in specific body tissue, such as heart ventricle, defined by the promoter incorporated into the gene switch. Thus, a person of ordinary skill in the art would not have looked to the Tang *et al.* reference for teachings relevant to the preparation of Applicants' claimed invention.

Moreover, Applicants respectfully maintain that the cited references do not teach or suggest a mammalian tissue comprising a genetically modified mammalian stem or progenitor cell as claimed in claims 28-34. There is no teaching or suggestion in any of the cited references to provide mammalian tissue with a genetically modified stem cell or progenitor cell of the invention. As noted above, the Tang *et al.* reference is concerned with direct gene therapy in a tissue and is not conceived with cell therapy. Thus, Tang *et al.* is only relevant with regard to transforming cells already present

within a tissue with a nucleic acid vector. As noted previously, the intended use of the genetically modified stem cell or progenitor cell is discussed to point out why a person of ordinary skill in the art would not look to the teachings of the cited references, *i.e.*, because they are directed to uses that are not relevant to the claimed invention. It was only the inventors of the claimed invention that realized the problem to be solved and did so by invention of the claimed genetically modified cell and mammalian tissue comprising the genetically modified cell.

Moreover, even assuming, *arguendo*, that the cited references did suggest modifying stem cells as recited in the claimed invention (which Applicants deny), Applicants respectfully assert that an ordinarily skilled artisan would not have had the requisite reasonable expectation of success. Applicants respectfully assert that there is no evidence that genetic modification with exogenous polynucleotides of the invention could be successfully applied to stem cells.

Applicants also maintain that the secondary references, Turgeman *et al.*, Juan *et al.*, and Nicklin *et al.*, cited under the §103 rejections fail to cure or overcome the deficiencies of Tang *et al.*, the primary reference. The Juan *et al.* reference is irrelevant as it does not teach or suggest that heme oxygenase 1 is cell protective against apoptosis. Thus, Applicants maintain that an ordinarily skilled artisan would not have looked to use a polynucleotide encoding heme oxygenase 1 in a genetically modified stem or progenitor cell of the claimed invention.

As the Examiner is aware, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must generally find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art and from the general knowledge in the art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). One finds neither the suggestion, nor the reasonable expectation of success, of Applicants' claimed invention in the cited references. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

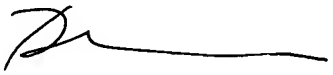
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachment: Petition and Fee for Extension of Time